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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/606,300
Filing Date: June 25, 2003
Appellant(s): PORRO ET AL.

Raymund F. Eich
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 30, 2007 appealing from the Office action mailed October 6, 2006.

(1) Real Party in Interest

The real party in interest of the present application is Universita Degli Studi di Milano, Bicocca, having a place of business at Piazza dell'Ateneo Nuovo I, Milano (Milan), Italy 20126.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

Receipt of the terminal disclaimer filed 10/20/2006 is acknowledged. The terminal disclaimer is sufficient to overcome the non-statutory obviousness-type double patenting rejection of claims 12-14 over claims 1-9 of U.S. Patent No. 6,630,330.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Smirnoff, N. "Ascorbic Acid: Metabolism and Functions of a Multi-Facetted Molecule" Current Opinion in Plant Biology, Vol. 3, No. 3 (June 2000), pp. 229-235.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-14 are drawn to methods of making ascorbic acid (vitamin C) comprising the use of recombinant yeast capable of converting any ascorbic acid precursor into L-ascorbic acid, wherein the yeast is functionally transformed with any one of a set of L-galactose dehydrogenase (LGDH) nucleic acids encoding LGDH enzymes having at least about 90% similarity to SEQ ID NO:11, a set of nucleic acids encoding LGDH enzymes having at least about 90% identity to SEQ ID NO:11, or having at least about 90% identity with SEQ ID NO:12. Thus the claims comprise a set of coding regions/amino acids defined by the function of the encoded protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide

sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes one nucleic acid sequence for LGDH and one protein sequence for LGDH wherein both sequences are from the mustard plant *Arabidopsis thaliana* (page 13, lines 10-13). No description is provided of any other LGDH sequences that result in a functionally transformed yeast cell capable of converting any ascorbic acid precursor into ascorbic acid or of any structure or sequence motifs that such LGDH sequences would share.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one LGDH from one source (*A. thaliana*). The results are not necessarily predictive of any other LGDH sequence. Thus, it is impossible for one of ordinary skill in the art to extrapolate from the one nucleic acid and the one amino acid sequence described herein those sequences that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of LGDH enzymes with 90% similarity or 90% identity to SEQ ID NO:11. A review published shortly before the effective date of the instant application describes an L-galactose dehydrogenase discovered in the pea plant and *A. thaliana* as a "newly discovered NAD^+-dependent L-galactose dehydrogenase" and further states that the enzyme is "as far as we know, the only plant dehydrogenase acting on a non-phosphorylated sugar" (see Smirnoff at page 230, paragraph bridging first and second columns). The review further teaches that the enzyme has been purified and cloned, but the data is unpublished (ibid).

Given the very large genus of sequences encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to their common sequence motifs/structures, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of LGDH sequences with 90% similarity or 90% identity with SEQ ID NOS: 11 and 12. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those embodiments that satisfy the functional

limitations of the claimed genus of LGDH enzymes with regard to their capability to convert any ascorbic acid precursor or set of ascorbic acid precursors into ascorbic acid as the LGDH of SEQ ID NO:11 does. Therefore, the skilled artisan would have reasonably concluded Appellants were not in possession of the claimed invention for claims 12-14.

(10) Response to Argument

Appellants argue that Examiner's inquiries with regard to the identification of deleterious vs. functional LGDH variants encompassed within the genus of those LGDH enzymes with 90% similarity and/or 90% identity to SEQ ID NO: 11 and those LGDH enzymes encoded by nucleic acids with 90% identity to SEQ ID NO:12 imply that Examiner has "read the written description requirement as *per se* requiring Applicants to present multiple sequences usable in the claimed method" (see page 5, 1st paragraph of the Appeal Brief filed 1/30/2007).

The prosecution history, however, makes clear that the rejection of the claims as failing to comply with the written description requirement was not based upon such a presumption. While an inquiry into functional vs. deleterious sequences was appropriately included in the Examiner's written description analysis, the analysis was by no means limited to the sequences

disclosed in the specification. As will be clear from the record, the analysis included a consideration of the complete or partial structure disclosed, physical and/or chemical properties, functional characteristics, and any structure/function correlation among the claimed LGDH variants capable of use in Appellant's method of producing ascorbic acid. The record also makes clear that Examiner considered the knowledge available to one of ordinary skill in the art at the time of filing, including an inquiry into any disclosed functional domains and/or sequence motifs characteristic of an LGDH enzyme such that, based upon Appellant's single example, one of ordinary skill in the art would recognize a functional LGDH variant with 90% similarity or 90% identity to Appellant's disclosed sequence. Because the prior art was found deficient with regard to disclosure of such LGDH sequences, much less those LGDH sequences capable of use in a method of converting any precursor into vitamin C upon transformation into a yeast, a greater degree of importance was placed upon the sequence disclosure in the specification. That is because, absent other art, one of ordinary skill in the art would rely exclusively upon Appellant's specification for description of any member of the genus of LGDH enzymes with 90% identity and/or similarly to SEQ ID NO:11 capable of use in the claimed methods.

Appellants cite the specification at page 19, lines 16-18 for a definition of LGDH as "a protein that catalyzes the conversion of L-galactono-1,4-lactone + 2 ferricytochrome c to L-ascoribc acid + 2 ferrocytochrome c" (see also page 5, 2nd full paragraph of the Appeal Brief filed 1/30/2007). Appellants further argue that "any protein which catalyzes the stated reaction is an L-galactose dehydrogenase, or LGDH" (ibid). Appellants further argue that this contention is supported by the reference to LGDH by its Enzyme Commission (EC) number "Enzyme 1.3.2.3" at page 19, line 16 of the specification, and that one skilled in the art would understand that such designation refers not to a particular protein but to a specific reaction catalyzed by any protein (ibid). Thus, Appellant argues, "L-galactose dehydrogenase" or "LGDH" was a term "having a plain and precise meaning well-known in the art as of the priority date of the present application" (ibid).

Examiner finds this line of argumentation to be confusing. The specification does not define LGDH as Appellant asserts; the definition cited by Appellant is that for a different enzyme: L-galactono-1,4-lactone dehydrogenase, an enzyme also referred to by Appellant as "AGD" (see specification at page 19, lines 16-18, and page 23, lines 19-20). Furthermore, the specification does not provide an EC number for LGDH, but rather teaches that

L-galactose dehydrogenase is an enzyme for which a classification number was not available in the databases (see specification at page 19, line 30 and page 20, line 25). Indeed, the specification lacks a definition for LGDH, although it is clear from the record that Examiner understood LGDH to refer to an enzyme which converts L-galactose to L-galactono-1,4-lactone (see, e.g., page 6, 1st paragraph, lines 1-6; and page 7, 2nd full paragraph, lines 10-14 of the action mailed 5/23/2006).

Appellants also argue that claim 12 complies with the written description requirement as supported by the present specification in light of the holdings in *Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Circ. 2005). Appellants and Examiner agree that the number of enzymes included in the genus of LGDH enzymes is large. Even if one includes only those LGDH enzymes with 90% identity to SEQ ID NO:11, the genus encompasses more than 3.4×10^{41} sequences according to Appellant's own calculations (see page 6, 2nd full paragraph of the Appeal Brief). Appellants further argue that listing every such sequence is impossible and that such a listing is not required. In support of this assertion Appellants argue that the Court held in *Capon v. Eshhar* that there is no *per se* rule that a sequence listing must be present for every biological sequence claimed in a patent

application (76 USPQ2d at 1084-1085). Appellants further assert that many of the Examiner's arguments in the final Office action are related to claim scope, e.g. the skilled artisan would not know which embodiments encompassed within the claimed genus of enzymes are functional in a method of making ascorbic acid and which are not, and that the claims merely provide an invitation to experiment to determine which sequences would meet the functional limitations of the claims. Appellants argue that Examiner alleged that the inclusion of non-operable embodiments showed the generic claims lack written description, and that such an allegation is incorrect because 1) the claims are plainly drawn to *LGDH* enzymes with 90% similarity or 90% identity to SEQ ID NO:11, *not* to *all* proteins having at least about 90% similarity/identity with SEQ ID NO:11; 2) *Capon v. Eshhar* addressed what is needed to support gene claims and held "it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention (at 1085); and 3) Examiner's "invitation to experiment" argument appears to concern enablement and not written description as held by the Federal Circuit Court in *Capon v. Eshhar* at 1086: "The Board's

position that the patents at issue were merely an 'invitation to experiment…' concerns enablement more than written description."

These arguments are not persuasive for a number of reasons. To begin, the instant case distinguishes itself from *Capon v. Eshhar* in several respects. Most saliently, in *Capon v. Eshhar* the invention did not concern the discovery of a newly discovered gene function and structure; instead the claims at issue were drawn to chimeric genes prepared from known DNA sequences of known function (page 1085, 1st full paragraph). In *Capon v. Eshhar* the Court held that the Board of Patent Appeals and Interferences erred in its requirement that the structure or formula or chemical name for a nucleotide sequence be reiterated in the specification even though such structures were already known and established in the public domain (ibid). Indeed, the parties in *Capon v. Eshhar* presented expert witnesses who, in placing the invention in the context of the prior knowledge and in explaining how the descriptive text would be understood by one or ordinary skill in the field of the invention, explained that "the prior art contains extensive knowledge of the nucleotide structure of the various immune-related segments of DNA" and that "over 785 mouse antibody DNA light chains and 1,327 mouse antibody DNA heavy chains were known and published…" (see paragraph bridging pages 1082-1083). *Capon v. Eshhar* did

not address a situation wherein the claims recite a large genus of sequences with a particular function and wherein written description support for such genus was based upon the disclosure of one novel sequence (SEQ ID NO:11) as is the case here.

Furthermore, in *Capon v. Eshhar* the Court did not find fault with the Board's contention that the patents at issue were merely an "invitation to experiment" *per se*, but rather found that, *in the context of the claims at hand, such an analysis did not distinguish among broad and narrow claims* (see page 1086, 3rd full paragraph). In *Capon v. Eshhar* the Court held that the Board erred because it "did not discuss the evidence with respect to the generality of the invention and the significance of the specific examples, instead simply rejecting all the claims for lack of a complete chimeric DNA sequence" (see page 1086, 3rd full paragraph). In the instant case, each of the claims at issue were properly assessed for written description support as could be found in the examples and teachings of the specification and in the prior art. Examiner found written description support lacking for claims drawn to a large genus of LGDH enzymes or nucleic acids which encode such enzymes based upon a structure/function analysis. Because all the claims at issue are drawn to such a large genus, the written description analysis performed by Examiner is appropriately applied to each

of the claims at issue. Appellants' support for the large genus of LGDH enzymes or nucleic acids which encode such enzymes in the instant case is based upon disclosure of one novel sequence disclosed in the specification and one art-recognized function: conversion of L-galactose into L-galactono-1,4-lactone. The prior art does not disclose any functional domains or motifs capable of guiding one of skill in the art to distinguish or envisage a variant with 90% similarity or 90% identity to SEQ ID NO:11 *capable of converting any precursor into ascorbic acid upon transformation into yeast*. Appellants have been invited to provide such information but have so far not addressed Examiner's concern in this regard.

Appellants correctly state that their invention is not drawn to all sequences with 90% identity or 90% similarity to SEQ ID NO:11, but rather plainly drawn to *LGDH* enzymes with 90% similarity or 90% identity to SEQ ID NO:11. Appellants also correctly teach that it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. Examiner has never argued otherwise. Examiner's assertions are based upon the lack of structural/functional information present in the prior art and instant specification

for one of skill in the art to envision those LGDH enzymes with 90% similarity or 90% identity to SEQ ID NO:11 capable of converting any ascorbic acid precursor or set of ascorbic acid precursors into ascorbic acid as the LGDH of SEQ ID NO:11 does. MPEP 2163 supports such an assertion wherein the written description guidelines indicate that

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the

> invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) (Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.)

(emphasis added). A rejection of the claims as lacking written description support seems appropriate in the instant case where Appellants have sought a method of making ascorbic acid from any vitamin C precursor or set of precursors with a yeast cell transformed with any nucleic acid encoding an LGDH enzyme with 90% similarity to that of SEQ ID NO:11 (representative of a genus which includes 3.4×10^{41} sequences according to Appellant's own calculations), and wherein the only known molecular function for such an enzyme is its ability to convert L-galactose into L-galactono-1,4-lactone. MPEP 2603 also states that

> What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide

> individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. Cf. In re Bell, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, para. 1.

(emphasis added). Thus, because the instant invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (*Mycolgen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001)), and given the deficiencies with regard to what was known about the ability of LGDH to increase ascorbic acid production in yeast, a representative number of species was not disclosed by Appellants and lack of written description was appropriately found.

In conclusion, it is not unreasonable for Examiner to have considered the scope of the claims (genus) in the written description analysis or to consider factors which overlap with factors considered in an enablement rejection of the claims

under 35 U.S.C. 112, 1st paragraph. Indeed, any rejection made under this statute must take into account the breadth of the claims, the teachings in the specification and the state of the art as well as the knowledge of one skilled in the field of the invention. Furthermore, Examiner has never alleged that the inclusion of non-operable embodiments showed the generic claims lack written description. Case law has made clear that an applicant's claims may include non-operable embodiments (see, e.g., *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976) and MPEP 2164.08(b)). Instead, Examiner finds that there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those embodiments that satisfy the functional limitations of the claimed genus of LGDH enzymes with regard to their capability to convert any ascorbic acid precursor or set of ascorbic acid precursors into ascorbic acid as the LGDH of SEQ ID NO:11 does. Therefore, the skilled artisan would have reasonably concluded Appellants were not in possession of the claimed invention for claims 12-14.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

Walter Schlapkohl

Examiner 1636

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